REMARKS

This is in response to the Office Action mailed on January 28, 2004, and the references cited therewith.

Claim 53 was amended, claims 1-52 and 69 are canceled, and claims 70-80 are added; as a result, claims 53-57, 64-65 and 70-80 are now pending in this application.

Preliminary Remarks:

Claim 53 is amended to more clearly identify the subject matter that is claimed.

New claims 70-80 are directed to the disclosed isolated antisense oligonucleotide that is complementary to at least a portion of a gene encoding a peripheral-type benzodiazepine receptor (PBR) that comprises the PBR amino acid sequence shown in SEQ ID NO:3; which antisense oligonucleotide inhibits the expression of said PBR gene when it is introduced into a mammalian cell that expresses said PBR gene, and thereby inhibits proliferation of said cell relative to an otherwise identical cell which does not contain said antisense oligonucleotide. New claim 75 specifies that the claimed antisense oligonucleotide is complementary to a portion of a PBR gene that encodes a fragment of a PBR protein shown in SEQ ID NO:3 that comprises the mutant residues threonine 147 and arginine 162. Support for these claims is found in the specification, for example, at page 15, line 25, to page 16, line 6. New claims 70 and 76 specify an antisense oligonucleotide that comprises a nucleotide sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:2. New claims 71 and 77 specify that the antisense oligonucleotide inhibits the proliferation of a human breast cancer cell containing a PBR protein that comprises the amino acid sequence shown in SEQ ID NO:3 when the oligonucleotide is introduced into said cell. New claims 72, 73, and 78-80 specify that the antisense oligonucleotide is encoded by a vector and is synthesized in a mammalian cell, *e.g.*, a human breast cancer cell, following introduction of said vector into said cell. Support for these new claims is found in the specification, for example, at page 25, line 28, to page 26, line 28.

Patentability Remarks:

Objections:

The official action objected to claim 53 for a grammatical error ("are having..."). Claim 53 has been amended to remove the error, and withdrawal of the objection is respectfully requested.

35 U.S.C. §112, First Paragraph

Claims 53-57 and 64-67 were rejected under 35 U.S.C. §112, First Paragraph, because the specification allegedly does not enable a person skilled in the art to make or use the claimed antisense oligonucleotide that inhibits expression of the disclosed cancer-associated PBR gene in a cell that expresses said PBR gene. The applicants respectfully traverse the rejection.

At the time the priority application was filed, it was well known by persons skilled in the art to which the claimed invention pertains that oligonucleotide sequences complementary to a selected gene that inhibit expression of the gene can be identified by synthesizing oligonucleotides that hybridize to overlapping target nucleotide sequences that cover a significant portion of the gene of interest, and by screening to identify the oligonucleotides that have inhibitory activity. Accordingly, while the inhibitory activity of any given oligonucleotide may be unpredictable, one of skill in the art would reasonably expect to identify one or more nucleotide sequences within the targeted gene where binding of an antisense oligonucleotide results in inhibition of the expression of the target gene.

The amended and new claims are also directed to relatively large oligonucleotideS that comprise a nucleotide sequence selected from the group consisting of SEQ ID NO:1 and SEQ ID NO:2, and to such oligonucleotides that are encoded by an expression vector and are synthesized in a mammalian cell following introduction of said vector into the cell. At the time the priority application was filed, methods for making and using vectors encoding large cDNAs to inhibit expression of a complementary target gene were well known in the art. Moreover, the scientific literature contains many reports showing that vector-mediated expression of a large cDNA complementary to a target gene in a mammalian cell inhibits the expression of the target gene. For example, see Ellis et al. (J Biol Chem. 1998 Jan 9; 273(2):1052-7), Waki et al. (Biochem Biophys Res Commun. 1994 Jun 15;201(2):1001-7), Rutka et al. (Cancer Res. 1994 Jun 15;54(12):3267-72), and Resnicoff et al. (Cancer Immunol Immunother. 1996 Jan;42(1):64-8) (abstracts attached), to name but a few. In contrast, reports of unsuccessful attempts to inhibit

the expression of the target gene in a cell by vector-mediated expression of a large cDNA complementary to a target gene are practically non-existent. In view of the numerous published reports describing inhibition of the expression of a target gene by vector-mediated expression of an antisense cDNA, persons of skill in the art would reasonably have expected that the vector-mediated expression of a large cDNA complementary to a target PBR gene in a cell, such as a cDNA comprising SEQ ID NO:1 or SEQ ID NO:2 would similarly successfully inhibit the expression of the target PBR gene.

In view of the foregoing, the applicants submit that the specification would enable persons of skill in the art to make and use the claimed antisense oligonucleotides to inhibit expression of the disclosed mutant PBR gene without the need to perform undue experimentation. Withdrawal of the rejection of the claims under 35 U.S.C. §112, First Paragraph, is therefore respectfully requested.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

Vassilios Papadopoulos

By their Representatives,

SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.
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(612) 373-6959

Date September 27 2004 By _____
Janet E. Embretson
Reg. No. 39,665

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 27th day of September, 2004.

PATRICIA A. HULTMAN
Name

_____
Signature

Attachments:

1) copies of abstracts of the following scientific articles:

a) Ellis et al. (J Biol Chem 1998 Jan 9;273(2):1052-7),

b) Waki et al. (Biochem Biophys Res Commun. 1994 Jun 15;201(2):1001-7),

c) Rutka et al. (Cancer Res. 1994 Jun 15;54(12):3267-72), and

d) Resnicoff et al. (Cancer Immunol Immunother. 1996 Jan;42(1):64-8).

2) A Form PTO 1449 listing the above-cited abstracts.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (612) 373-6903 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

Vassilios Papadopoulos

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Date _____ By _____
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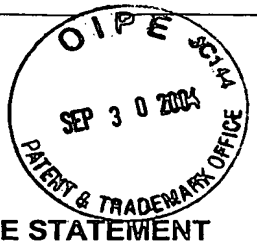

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Applicant: PAPADOPOULOS et al.

Appln. No.: 09/047,652

Filing Date: March 25, 1998

Date: July 28, 2004 Page 1 of 1

Examiner: M. DAVIS Group Art Unit: 1642

U.S. PATENT DOCUMENTS

Examiner's Initials*		Document Number	Date MM/YYYY	Name (Family Name of First Inventor)	Class	Sub Class	Filing Date (if appropriate)
	AR						
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	RR									
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	TR									
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OTHER (Including in this order Author, Title, Periodical Name, Date, Pertinent Pages, etc.)

	WR	Ellis et al., J Biol Chem. 1998 Jan 9;273(2):1052-7, Abstract only.
	XR	Resnicoff et al., Cancer Immunol Immunother. 1996 Jan;42(1):64-8, Abstract only.
	YR	Rutka et al., Cancer Res. 1994 Jun 15;54(12):3267-72, Abstract only.
	ZR	Waki et al., Biochem Biophys Res Commun. 1994 Jun 15;201(2):1001-7, Abstract only.
	AAR	
	BBR	

Examiner Date Considered:

*EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP § 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to Applicant.

☐ 1: J Biol Chem. 1998 Jan 9;273(2):1052-7. Related Articles, Linl

Down-regulation of vascular endothelial growth factor in a human colon carcinoma cell line transfected with an antisense expression vector specific for c-src.

Ellis LM, Staley CA, Liu W, Fleming RY, Parikh NU, Bucana CD, Gallick GE.

Department of Surgical Oncology, University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030, USA.

Vascular endothelial growth factor (VEGF) is implicated in the angiogenesis of human colon cancer. Recent evidence suggests that factors that regulate VEGF expression may partially depend on c-src-mediated signal transductio pathways. The tyrosine kinase activity of Src is activated in most colon tumors and cell lines. We established stable subclones of the human colon adenocarcinoma cell line HT29 in which Src expression and activity are decreased specifically as a result of a transfected antisense expression vector. This study determined whether VEGF expression is decreased in these cell lines and whether the smaller size and reduced growth rate of antisense vector-transfected cell lines in vivo might result, in part, from reduced vascularization of tumors. Northern blot analysis of these cell lines revealed that VEGF mRNA expression was decreased in proportion to the decrease in Src kinase activity. Under hypoxic conditions, cells with decreased Src activity had a <2-fold increase in VEGF expression, whereas parental cells had a >50-fold increase. VEGF protein in the supernatants of cells was also reduced in antisense transfectants compared with that from parental cells. In nude mice, subcutaneous tumors from antisense transfectants showed a significant reduction in vascularity. These results suggest that Src activity regulates the expression of VEGF in colon tumor cells.

PMID: 9422768 [PubMed - indexed for MEDLINE]

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1: Biochem Biophys Res Commun. 1994 Jun 15;201(2):1001-7.

Antisense src expression inhibits U937 human leukemia cell proliferation in conjunction with reduction of c-myb expression.

Waki M, Kitanaka A, Kamano H, Tanaka T, Kubota Y, Ohnishi H, Takahara J, Irino S.

First Department of Internal Medicine, Kagawa Medical School, Japan.

To elucidate the role of pp60c-src in U937 human monoblastoid leukemia ce proliferation, recombinant plasmids containing the src gene or myb gene, which could produce antisense src or antisense myb RNA after dexamethasone treatment, were constructed and transfected into U937 cells (U937-ASRC, U937-AMYB). pp60c-src synthesis in U937-ASRC was diminished by the third day after induction of antisense src RNA and the cell proliferation was reduced, furthermore, the amount of p75c-myb was significantly decreased by the third day. p75c-myb synthesis in U937-AMYI was diminished by the second day after induction of antisense myb RNA and the cell growth was significantly inhibited but the amount of pp60c-src in U937-AMYB was not reduced. These results suggest that a decrease in the amount of pp60c-src leads to an inhibition of p75c-myb expression and subsequent reduction in the U937 cell proliferation.

PMID: 7516155 [PubMed - indexed for MEDLINE]

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1: Cancer Res. 1994 Jun 15;54(12):3267-72.

Effects of antisense glial fibrillary acidic protein complementary DNA on the growth, invasion, and adhesion of human astrocytoma cells.

Rutka JT, Hubbard SL, Fukuyama K, Matsuzawa K, Dirks PB, Becker LE.

Brain Tumor Research Laboratory, Hospital for Sick Children, University of Toronto, Ontario, Canada.

Glial fibrillary acidic protein (GFAP)-positive astrocytoma cells were stably transfected with an expression vector carrying a murine complementary DNA for GFAP in the antisense orientation. Three stably transfected GFAP-negative transformants were identified by indirect immunofluorescence and expanded in vitro. The stably transfected and control cell clones were analyzed for morphological alterations, growth in monolayer and soft agar, adhesiveness, and in vitro invasive potential. In contrast to control astrocytoma cells which retained an astrocytic phenotype with polygonal or triangular cells extending multiple long and thin processes, the antisense GFAP-transfected cells demonstrated marked morphological alterations in th form of flat, epithelioid cells devoid of long, astrocytic glial processes. The antisense GFAP-transfected clones demonstrated a greater degree of cell crowding and piling at confluence than did controls. By tritiated thymidine analysis, the antisense GFAP-transfected cell clones demonstrated a 2-3-fold increase in incorporation of the radiolabel, suggesting an enhanced proliferative potential over controls. Antisense GFAP-transfected astrocytom clones formed larger and more numerous colonies than did controls when tested for anchorage-independent growth in soft agar. Following a time-course adhesion assay, antisense GFAP-transfected astrocytoma clones were found to be less adherent to their substratum than controls. When assessed in an in vitro invasion assay system, antisense GFAP-transfected astrocytoma cells more readily penetrated Matrigel-coated filters than did controls. These data have shown that eliminating GFAP expression from astrocytoma cells has affected astrocytoma cell morphology and adhesion. The data also sugge that the growth and invasive potential of the antisense GFAP-transfected astrocytoma cells have been significantly enhanced by altering the expressio of this glial-specific cytoskeletal protein in this experimental cell system.

☐ 1: Cancer Immunol Immunother. 1996 Jan;42(1):64-8.

Inhibition of rat C6 glioblastoma tumor growth by expression of insulin-like growth factor I receptor antisense mRNA.

Resnicoff M, Li W, Basak S, Herlyn D, Baserga R, Rubin R.

Jefferson Cancer Institute, Philadelphia, PA 19104, USA.

The expression of insulin-like growth factor I receptor (IGF-IR) antisense mRNA inhibits the growth of C6 rat glioblastoma cells both in vitro and in vivo [Cancer Res (1994) 54:2218]. Moreover, the injection of C6 cells expressing an antisense mRNA to the IGF-IR into syngeneic rats prevents subsequent wild-type tumorigenesis and induces regression of established tumors. For the study of immune function in syngeneic rats, C6 cells expressing either IGF-IR sense or IGF-IR antisense mRNA were injected and splenic lymphocyte function analyzed in vitro after 2 weeks. Cytotoxic, CD8 lymphocytes from animals injected with IGF-IR antisense cells, but not from those treated with IGF-IR sense cells, proliferated in vitro in response to wild type C6 cells. Wild-type C6 cells or IGF-IR-sense-RNA-expressing cells rapidly formed tumors upon subcutaneous injection into athymic nude mice. IGF-IR antisense cells were weakly tumorigenic, exhibiting a six- to tenfold increase in tumor latency. Injection of IGF-IR antisense C6 cells mildly delayed the development of wild-type tumors, and did not induce the regression of established wild-type C6 tumors in athymic nude mice. Thus, these findings demonstrate the stimulation of a cellular immune response in rats following the injection of IGF-IR antisense cells. However, studies of athymic nude mice indicate that expression of IGF-IR antisense mRNA also inhibits C6 cells tumorigenicity by additional mechanisms.

PMID: 8625368 [PubMed - indexed for MEDLINE]

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